Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Article

Impact of Hyperglycemia on Cardiovascular Events and Clinical Outcomes in Patients Hospitalized With COVID-19 Pneumonia

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ABSTRACT

Objective: To study cardiovascular events and clinical outcomes in patients with elevated glycated hemoglobin (HbA1c) levels and/or admission hyperglycemia and those with type 2 diabetes hospitalized with SARS-CoV-2 pneumonia.

Methods: This was a multicenter retrospective study of 1645 patients hospitalized with SARS-CoV-2 pneumonia. Diagnosis of SARS-CoV-2 pneumonia required a positive reverse transcription-polymerase chain reaction result for SARS-CoV-2, presence of new or worsening pulmonary infiltrates on computed tomography scan or chest x-ray, and at least one of following: (1) new or increased cough, (2) temperature of >37.8 °C, or (3) dyspnea. Outcomes included in-hospital cardiovascular events, intensive care unit admission, and mortality. Logistic regression was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for association of elevated HbA1c levels and/or admission hyperglycemia and type 2 diabetes for individual outcomes.

Results: Among 1645 adults hospitalized with SARS-CoV-2 pneumonia, 18 with type 1 diabetes were excluded from the analysis. Of 1627 adults, 634 (39%) had known diagnosis of type 2 diabetes, and among 993 patients with no diabetes, 107 (10.8%) patients were identified with elevated HbA1c levels and/or admission hyperglycemia. Patients with elevated HbA1c levels and/or admission hyperglycemia had increased odds of developing acute in-hospital cardiovascular events (OR, 1.73; 95% CI, 1.07-2.80), intensive care unit admissions (OR, 1.61; 95% CI, 1.10-2.34), and mortality (OR, 1.77; 95% CI, 1.02-3.07) compared to patients with type 2 diabetes and no diabetes.

Conclusion: Patients with elevated HbA1c levels and/or admission hyperglycemia hospitalized with SARS-CoV-2 pneumonia have increased risk of developing acute in-hospital cardiovascular complications and overall poor clinical outcomes compared with patients with type 2 diabetes and no diabetes.

Introduction

Evidence from the pandemic of COVID-19 shows that the coexistence of type 2 diabetes in patients hospitalized with SARS-CoV-2 can worsen disease prognosis.[1,2] As the pandemic evolved, it became clear that hyperglycemia independently predisposes patients with SARS-CoV-2 pneumonia to adverse outcomes,[3-6] irrespective of an underlying history of diabetes. Hyperglycemia is a common finding in critical illness, including community-

Abbreviations: CI, confidence interval; CHF, congestive heart failure; CVA, cerebrovascular accident; EHR, electronic health record; HbA1c, glycated hemoglobin; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; MI, myocardial infarction; OR, odds ratio.

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acquired pneumonia, and is an important predictor of mortality.[7,8] Hyperglycemia in patients with SARS-CoV-2 can be indicative of preexisting diabetes, undiagnosed diabetes, steroid-induced stress hyperglycemia, or new-onset COVID-19–triggered diabetes related to direct beta cell injury.[9,10] Hyperglycemia can also be associated with SARS-CoV-2 infection without the diagnosis of diabetes. Regardless of etiology, glycemic excursions can complicate the management and increase susceptibility to severe disease outcomes.

Admission hyperglycemia and higher glycated hemoglobin (HbA1c) levels have shown to be associated with poor outcomes in patients with SARS-CoV-2.[11,12] Although some studies have assessed the impact of undiagnosed diabetes in patients with SARS-CoV-2,[3–5] there is limited evidence concerning the consequences of elevated HbA1c levels and/or admission hyperglycemia on cardiovascular outcomes. In the present study, we investigated the cardiovascular events and clinical outcomes in patients with elevated HbA1c levels and/or admission hyperglycemia and type 2 diabetes hospitalized with SARS-CoV-2 pneumonia.

Highlights

- Patients with elevated glycated hemoglobin (HbA1c) levels and/or admission hyperglycemia hospitalized with SARS-CoV-2 pneumonia have increased risk of developing cardiovascular complications and death
- Patients with elevated HbA1c levels and/or admission hyperglycemia require aggressive in-hospital management, including an increased need for intensive care unit admission, vasopressor, and invasive mechanical ventilation
- Accentuated risk of cardiovascular complications and overall poor prognosis in patients with elevated HbA1c levels and/or admission hyperglycemia may be related to dysfunctional prothrombotic and inflammatory state due to SARS-CoV-2 in setting of uncorrected hyperglycemia

Clinical Relevance

Among patients hospitalized with SARS-CoV-2 pneumonia, those presenting with elevated glycated hemoglobin levels and/or new-onset admission hyperglycemia warrant closer attention owing to the higher risk of cardiovascular complications and poor clinical outcomes.

Methods

Study Design

This is a retrospective study of hospitalized patients diagnosed with COVID-19 between March 7, 2020, and March 30, 2021, in 8 adult acute-care hospitals.

Study Population

We selected patients who were hospitalized with SARS-CoV-2 pneumonia from the electronic health record (EHR). The inclusion criteria for SARS-CoV-2 pneumonia were a positive reverse transcription-polymerase chain reaction result for SARS-CoV-2, presence of new or worsening of pulmonary infiltrates on computed tomography scan or chest x-ray, and at least 1 of the following: (1) new or increased cough, (2) temperature of >37.8 °C, or (3) dyspnea.

The history of diabetes was extracted from the EHR, along with the type of diabetes and insulin treatment status. Patients with gestational diabetes, type 1 diabetes, and steroid-induced hyperglycemia were excluded. Supplementary Figure 1 depicts a flowchart of the study population.

Study Group Definition

Patients with elevated HbA1c levels and/or admission hyperglycemia had a HbA1c level of ≥6.5% (48 mmol/mol) or an admission serum glucose level of ≥200 mg/dL (≥11.1 mmol/mol) with no previous history of diabetes. The study population hospitalized with SARS-CoV-2 pneumonia was categorized into 3 groups. The first group consisted of patients who had elevated HbA1c levels and/or admission hyperglycemia. The second group consisted of patients who had established type 2 diabetes. The diagnosis of established type 2 diabetes was made using International Classification of Diseases, 10th Revision (E11.9). The third group consisted of patients with no current or past evidence of diabetes.

Protection of Human Subjects

The study was approved by the Institutional Review Board of the University of Louisville Human Subjects Research Protection Program Office. Research Electronic Data Capture, which is a secure software platform designed to support research studies,[13] was used to capture all patient health information.

Data Collection

Data collection from the EHR included demographics, comorbidities, current medications, physical examination, anthropometric, laboratory values, hospital management, in-hospital complications, and clinical outcomes.

Outcomes

The primary study outcomes included intensive care unit (ICU) admissions, in-hospital cardiovascular events, and all-cause mortality. The cardiovascular event variable was dichotomized as 1 or none. Cardiovascular events included new-onset heart failure, sudden cardiac arrest, acute myocardial infarction (MI), pulmonary edema due to congestive heart failure (CHF), pulmonary emboli, development of new serious arrhythmia, acute worsening of long-term arrhythmia, cerebrovascular accident (CVA), and cardiogenic shock. CVA included both ischemic stroke and hemorrhagic stroke. In-hospital mortality was defined as all-cause mortality occurring during the hospitalization.

Statistical Analysis

Descriptive statistics for relevant covariates were calculated to examine their distributions. Univariate analyses were conducted to examine the crude association between covariates and a history of type 2 diabetes. The χ^2 or Fisher exact tests were used for categorical variables; the 1-way analysis of variance test was used for normally distributed, continuous variables; and the Kruskal-Wallis test was used for nonnormally distributed, continuous variables. Continuous data are presented as mean ± SD if normally distributed or as median (interquartile range [IQR]) if not normally distributed. Categorical data are presented as percentages (%).

For the multivariate models, age was used as a continuous variable. Dichotomous variables included sex, obesity (body mass

index, ≥30 kg/m^2), nursing home residency, history of chronic obstructive pulmonary disease, neoplastic disease, cardiovascular diseases, CURB-65 (score, ≥3), and hypoxemia. Cardiovascular diseases included MI, CVA, CHF, and coronary artery disease. CURB-65 is a 6-point score that assigns 1 point for each of confusion, blood urea nitrogen level of >19 mg/dL, respiratory rate of ≥30 breaths/minute, low systolic (<90 mm Hg) or diastolic (≤60 mm Hg) blood pressure, and age of ≥65 years.[14] Hypoxemia was assessed by the ratio of arterial oxygen partial pressure—to—fractional inspired oxygen of <200 or ratio of oxygen saturation to a fraction of inspired oxygen of <141 if blood gases were not obtained.

Multivariate logistic regression was used to examine the effect of type 2 diabetes and elevated HbA1c levels and/or admission hyperglycemia on all 3 primary outcomes: (1) ICU admission, (2) in-hospital cardiovascular events, and (3) all-cause in-hospital mortality. All models were adjusted for the same set of covariates. Cluster robust SEs, using hospitals as clusters, were performed to account for within-hospital variation. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated and adjusted for potential confounders. *P* values of <.05 were considered statistically significant. A sensitivity analysis was also conducted, restricting the population to no diabetes to examine the effect of elevated HbA1c levels and/or admission hyperglycemia. All statistical analyses were performed using R Studio version 1.2.5033.[15]

Results

Of the 1645 adults hospitalized with SARS-CoV-2 pneumonia, 18 with type 1 diabetes were excluded from the analysis. A total of 634 (39%) of 1627 adults had a known history of type 2 diabetes, of whom 255 (40.9%) were insulin requiring. Among the 993 patients with no diabetes, 107 (10.8%) were identified with elevated HbA1c levels and/or admission hyperglycemia. The remaining 886 patients were identified as patients with no diabetes.

The baseline patient characteristics stratified by the 3 diabetes status groups are shown in Table 1. In comparison with patients with no diabetes, those with type 2 diabetes were older (median, 67 years; IQR, 58-75), more often obese (61%, n = 388), from Black race (33%, n = 212), and nursing home residents (15%, n = 95) (Table 1). Higher prevalence rates of renal disease (33%, n = 210), CHF (22%, n = 142), coronary artery disease (27%, n = 172), hyperlipidemia (58%, n = 369), essential hypertension (83%, n = 527), and prior MI (14%, n = 87) were noted in patients with type 2 diabetes group than in the other 2 groups. The uses of β-blockers (48%, n = 305), angiotensin-converting enzyme inhibitors (28%, n = 176), and statins (61%, n = 389) were more commonly observed in patients with type 2 diabetes than in the other 2 cohorts. Patients with type 2 diabetes presented more frequently with confusion (14%, n = 87) than those with elevated HbA1c levels and/or admission hyperglycemia and with no history of diabetes (Table 1).

Table 1
Baseline Characteristics of Patients at Admission Stratified by Diabetes Status, n = 1627

Variables	Elevated HbA1c levels and/or admission hyperglycemia	Type 2 diabetes	No diabetes	*P* value
	n = 107	n = 634	n = 886	
Age (y) (median [IQR])	63 [52-72]	67 [58-75]	62 [50-74]	<.001
Sex: male	62 (58)	326 (51)	429 (48)	.131
Obesity	67 (63)	388 (61)	421 (48)	<.001
Race				<.001
African American/Black	17 (16)	212 (33)	206 (23)	
Caucasian/White	78 (73)	381 (60)	578 (65)	
Other	12 (11)	41 (6)	102 (12)	
Hispanic ethnicity	9 (8)	36 (6)	86 (10)	.017
Nursing home residence	6 (6)	95 (15)	99 (11)	.029
Former smoker	36 (34)	247 (39)	277 (31)	.007
Current smoker	7 (7)	45 (7)	87 (10)	.129
Alcohol or drug abuse	7 (7)	40 (6)	93 (10)	.012
Past medical history				
Renal disease	16 (15)	210 (33)	101 (11)	<.001
Congestive heart failure	9 (8)	142 (22)	73 (8)	<.001
Coronary artery disease	15 (14)	172 (27)	120 (14)	<.001
Cerebrovascular disease	8 (7)	90 (14)	95 (11)	.041
Neoplastic disease (active or within the last year)	10 (9)	46 (7)	90 (10)	.147
COPD	20 (19)	135 (21)	130 (15)	.003
Liver disease	18 (17)	139 (22)	93 (10)	<.001
Essential hypertension	62 (58)	527 (83)	495 (56)	<.001
Hyperlipidemia	38 (36)	369 (58)	302 (34)	<.001
Prior myocardial infarction	9 (8)	87 (14)	56 (6)	<.001
Atrial fibrillation	7 (7)	93 (15)	91 (10)	.007
Aspirin	26 (25)	253 (40)	197 (22)	<.001
β-blockers	25 (24)	305 (48)	222 (25)	<.001
ACE inhibitors	19 (18)	176 (28)	113 (13)	<.001
Statins	35 (33)	389 (61)	253 (29)	<.001
Signs and symptoms at admission				
Fever/subjective fever	52 (49)	346 (55)	546 (62)	.003
Dyspnea	82 (77)	448 (71)	623 (70)	.393
Headache	12 (11)	61 (10)	123 (14)	.041
Confusion	8 (7)	87 (14)	77 (9)	.004
Cough	68 (64)	419 (66)	607 (69)	.429
Sputum production	20 (19)	101 (16)	135 (15)	.641

Abbreviations: ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; HbA1c= glycated hemoglobin; IQR = interquartile range.
Data are expressed as n (%) or median (IQR), unless otherwise indicated.

Patients with elevated HbA1c levels and/or admission hyperglycemia presented with a lower ratio of arterial oxygen partial pressure–to–fractional inspired oxygen (median, 115; IQR, 71.2-211.2) and higher serum glucose level (median, 208 mg/dL; IQR, 157-252) at admission than those with type 2 and no diabetes (Table 2). The inflammatory marker levels were elevated in both the elevated HbA1c level and/or admission hyperglycemia and type 2 diabetes groups except for ferritin levels, which were higher in the former group (median, 525 ng/dL; IQR, 321-934) than in type 2 diabetes. The HbA1c level was comparable in those with elevated HbA1c levels and/or admission hyperglycemia and type 2 diabetes (Table 2).

Among patients with elevated HbA1c levels and/or admission hyperglycemia, a higher proportion of patients needed ICU care than patient with type 2 diabetes (56%, n = 60, vs 39%, n = 249; $P <$ .001) or with no diabetes (33%, n = 296). Patients with elevated HbA1c levels and/or admission hyperglycemia were more frequently admitted directly to ICU from the emergency department than those with type 2 diabetes (33%, n = 35 vs 22%, n = 138; P = .001) or with no history of diabetes (18%, n = P = .001158) (Table 3). Among those admitted to the ICU, patients with elevated HbA1c levels and/or admission hyperglycemia had an increased need for invasive mechanical ventilation (IMV) compared with those with type 2 diabetes (44%, n = 47, vs 25%, n = 157; $P <$ .001). The need for IMV in this cohort was 2 times as much as those with no diabetes. We noted that those with elevated HbA1c levels and/or admission hyperglycemia more often needed systemic steroids during the hospital course. Patients with elevated HbA1c levels and/or admission hyperglycemia were more likely to have in-hospital complications, including development of acute respiratory distress syndrome (16%, n = 17), septic shock (19%, n = 20), and sudden cardiac arrest (9%, n = 10). In addition, they had a higher likelihood of dying or requiring hospice care than those with type 2 diabetes (32%, n = 34, vs 22%, n = 142), and the risk of dying was twice as high in those with hyperglycemia compared with that in patients with no diabetes (32%, n = 34, vs 15%, n = 135; $P <$ .001). Cardiovascular events were more prevalent in the cohort with elevated HbA1c levels and/or admission hyperglycemia (24%, n = 26) than in patients with type 2 diabetes or no diabetes (20%, n = 125, vs 13%, n = 114; $P <$ .001). The reported cardiovascular events in those with elevated HbA1c levels and/or admission hyperglycemia included development of new arrhythmias (10%, n = 11), sudden cardiac arrest (9%, n = 10), acute MI (5%, n = 5), heart failure (4%, n = 4), pulmonary embolism (3%, n = 3), CVA (3%, n = 3), pulmonary edema (2%, n = 2), cardiogenic shock (2%, n = 2), and worsening of long-term arrhythmias (1%, n = 1) (Table 3).

After adjusting for relevant confounders (age, sex, obesity, nursing home residency, history of chronic obstructive pulmonary disease, obstructive sleep apnea, atrial fibrillation, cardiovascular disease, CURB-65 of ≥3, and hypoxemia), patients with elevated HbA1c levels and/or admission hyperglycemia had increased odds of ICU admission (OR, 1.61; 95% CI, 1.10-2.34), development of cardiovascular events (OR, 1.73; 95% CI, 1.07-2.80), and mortality (OR, 1.77; 95% CI, 1.02-3.07) compared with those with no diabetes (Table 4, Fig.). A prior history of type 2 diabetes was not significantly associated with the observed study outcomes. In addition, sensitivity analyses retained similar significant increased odds of in-hospital mortality (OR, 1.51; 95% CI, 1.00-2.30) for those with elevated HbA1c levels and/or admission hyperglycemia compared with those with type 2 diabetes (Table 4, Fig.).

Discussion

Our study demonstrated that 10.8% of the patients hospitalized with SARS-CoV-2 pneumonia had elevated HbA1c levels and/or admission hyperglycemia with no prior history of diabetes. Among the patients hospitalized with SARS-CoV-2 pneumonia, the cohort with elevated HbA1c levels and/or admission hyperglycemia had a nearly twofold increased risk of developing acute cardiovascular events, requiring admission to ICU, and increased mortality comparison with those with type 2 diabetes and no diabetes. To the best of our knowledge, this is the first study to illustrate the association between an increased risk of cardiovascular events in patients hospitalized with SARS-CoV-2 pneumonia and elevated HbA1c levels and/or admission hyperglycemia. Compared with patients with type 2 diabetes, those with elevated HbA1c levels and/or admission hyperglycemia had an increased risk of mortality.

Previous studies have shown that patients with type 2 diabetes are at increased risk of poor outcomes with SARS-CoV-2 [2] Hyperglycemia-mediated inflammation and endothelial and immune dysfunction can be the driving force behind the adverse outcomes.[4] In our cohort, in an unadjusted model, patients with type 2 diabetes were associated with an increased mortality or need for hospice care and ICU admission compared with patients

Table 2
Physical Examination and Laboratory Values stratified by Diabetes Status, n = 1627

Variables	Elevated HbA1c levels and/or admission hyperglycemia	Type 2 diabetes	No diabetes	*P* value
	n = 107	n = 634	n = 886	
Respiratory rate (breaths/min)	24.0 [20.0-31.5]	23.0 [20.0-28.0]	22.0 [18.0-28.0]	.005
Systolic blood pressure (mm Hg)	119.0 [97.5-139.5]	125.0 [107.0-143.0]	120.0 [106.0-136.0]	.002
Diastolic blood pressure (mm Hg)	62.0 [50.0-76.5]	63.0 [53.0-76.0]	66.0 [55.0-77.0]	.009
SpO_2/FiO_2	285.7 [99.0-428.6]	335.7 [248.6-438.1]	402.4 [278.9-447.6]	<.001
PaO_2/FiO_2	115.0 [71.2-211.2]	218.2 [129.1-304.9]	228.6 [118.7-319.0]	<.001
Neutrophil/lymphocyte	9.6 [4.4-17.1]	6.3 [3.5-12.2]	5.5 [3.1-10.8]	<.001
Admission serum glucose (mg/dL)	208.0 [157.0-252.0]	176.0 [127.0-258.0]	116.0 [103.0-131.0]	<.001
HbA1c (%)	7.1 [6.7-8.1]	7.6 [6.5-9.3]	5.8 [5.5-6.1]	<.001
BUN (mg/dL)	21.0 [15.0-43.0]	25.0 [16.0-43.0]	16.0 [12.0-25.0]	<.001
Creatinine (mg/dL)	1.1 [0.8-2.0]	1.2 [0.9-2.0]	1.0 [0.7-1.3]	<.001
Ferritin (ng/dL)	525.0 [321.0-934.0]	387.0 [178.0-836.0]	402.5 [169.8-809.0]	.049
Procalcitonin (ug/L)	0.2 [0.1-0.5]	0.2 [0.1-0.7]	0.1 [0.1-0.4]	<.001
Lactate (mmol/L)	1.8 [1.4-3.3]	1.5 [1.1-2.1]	1.3 [1.0-1.8]	<.001
D-Dimer (ng/mL)	850.5 [313.2-2092.2]	870.0 [399.0-1718.5]	715.0 [362.2-1331.8]	.007
IL-6 (pg/mL)	41.2 [16.4-79.8]	48.7 [18.1-99.4]	29.9 [12.9-66.8]	.017
C-reactive protein (mg/L)	41.9 [14.1-136.0]	21.5 [7.8-78.0]	19.8 [6.3-63.22]	.002

Abbreviations: BUN= blood urea nitrogen; HbA1c= glycated hemoglobin; IL-6= interleukin 6; PaO_2/FiO_2 = arterial oxygen partial pressure–to–fractional inspired oxygen ratio; SpO_2/FiO_2 = oxygen saturation–to–fraction of inspired oxygen ratio; WBC = white blood cell.
Data are expressed as median and interquartile range.

Table 3
In-Hospital Events Stratified by Diabetes Status, n = 1627

Variables	Elevated HbA1c levels and/or admission hyperglycemia	Type 2 diabetes	No diabetes	*P* value
	n = 107	n = 634	n = 886	
ICU care	60 (56)	249 (39)	296 (33)	<.001
Direct ICU admission	35 (33)	138 (22)	158 (18)	.001
ICU LOS, days median [IQR]	11.0 [4.42-16.0]	6.13 [2.71-13.6]	8.00 [3.16-15.5]	.102
Treatments				
IMV	47 (44)	157 (25)	177 (20)	<.001
Remdesivir	48 (45)	233 (37)	303 (34)	.08
Plasma therapy	23 (21)	90 (14)	129 (15)	.135
Neuromuscular blockade	23 (21)	73 (12)	104 (12)	<.011
Vasopressors	39 (36)	140 (22)	143 (16)	<.001
Inotropes	10 (9)	64 (10)	68 (8)	.25
Systemic steroids	82 (77)	410 (65)	530 (60)	<.001
Events during hospital course				
ARDS	17 (16)	73 (12)	97 (11)	.318
Septic shock	20 (19)	78 (12)	87 (10)	.015
Mortality/hospice	34 (32)	142 (22)	135 (15)	<.001
Cardiovascular events	26 (24)	125 (20)	114 (13)	<.001
Types of cardiovascular events				
New arrhythmias	11 (10)	51 (8)	57 (6)	.234
Sudden cardiac arrest	10 (9)	28 (4)	15 (2)	<.001
Acute MI	5 (5)	24 (4)	14 (2)	.012
Heart failure	4 (4)	27 (4)	21 (2)	.113
Pulmonary embolism	3 (3)	11 (2)	15 (2)	.71
CVA	3 (3)	5 (1)	11 (1)	.191
Pulmonary edema	2 (2)	14 (2)	12 (1)	.445
Cardiogenic shock	2 (2)	9 (1)	9 (1)	.643
Worsening of long-term arrhythmias	1 (1)	14 (2)	19 (2)	.686

Abbreviations: ARDS = acute respiratory disease syndrome; CVA = cerebrovascular accident; ICU = intensive care unit; IMV = invasive mechanical ventilation; IQR = interquartile range; LOS = length of stay; MI = myocardial infarction.
Data are expressed as n (%) or median (IQR), unless otherwise indicated.

with no diabetes. However, after adjusting for confounders, that association was not significant. Similar findings have been reported in another study,[4] implying that aging with multiple underlying comorbidities can predispose patients with type 2 diabetes to poor outcomes. In our study, we noted that patients with type 2 diabetes frequently presented with confusion that could be related to uremia or neuroinvasive potential of SARS-CoV-2.

This study found that patients with elevated HbA1c levels and/or admission hyperglycemia had worse clinical outcomes than patients with type 2 diabetes and no diabetes. These patients required aggressive hospital management, including ICU admission, IMV, and vasopressors. Increased mortality, more frequent ICU admission, and mechanical ventilation have been reported by others;[16,17] however, little is known about cardiovascular events and complications in patients with elevated HbA1c levels and/or admission hyperglycemia and SARS-CoV-2 pneumonia. Our study revealed that those with elevated HbA1c levels and/or admission hyperglycemia had a higher risk of developing cardiovascular complications. The most frequent cardiovascular events included new arrhythmias, sudden cardiac arrest, acute MI, and heart failure. The accentuated risk of cardiovascular events and overall poor prognosis in these patients may be related to the dysfunctional prothrombotic and inflammatory state due to SARS-CoV-2 in the setting of acute hyperglycemia.

There are a few possible explanations for these differences in patients with elevated HbA1c levels and/or admission hyperglycemia and type 2 diabetes. Patients with an established diagnosis of diabetes may have received more intensive medical care and intervention for hyperglycemia before and at admission, whereas aggressive diabetes management may have been delayed in those with newly diagnosed diabetes. Additionally, those with established type 2 diabetes were more likely to be on angiotensin-converting enzyme inhibitors, β-blockers and statins before admission that may have contributed to better outcomes than

Table 4
Multivariate Logistic Regression for Study Outcomes Stratified by Diabetes Status, n = 1627

Variables	ICU admission	In-hospital cardiac event	In-hospital mortality
	Odds ratio[a] (95% CI)	Odds ratio[a] (95% CI)	Odds ratio[a] (95% CI)
No diabetes	1.00 (referent)	1.00 (referent)	1.00 (referent)
Type 2 diabetes	1.11 (0.88-1.41)	1.35 (0.98-1.86)	1.16 (0.93-1.45)
Elevated HbA1c levels and/or admission hyperglycemia	1.61 (1.10-2.34)[b]	1.73 (1.07-2.80)[b]	1.77 (1.02-3.07)[b]
Comparing patients with elevated HbA1c levels and/or admission hyperglycemia with those with no diabetes			
No diabetes	1.00 (referent)	1.00 (referent)	1.00 (referent)
Elevated HbA1c levels and/or admission hyperglycemia	1.52 (1.01-2.29)[b]	1.83 (1.15-2.92)[b]	1.81 (1.04-3.13)[b]
Comparing patients with elevated HbA1c levels and/or admission hyperglycemia with those with type 2 diabetes			
Type 2 diabetes	1.00 (referent)	1.00 (referent)	1.00 (referent)
Elevated HbA1c levels and/or admission hyperglycemia	1.50 (0.99-2.26)	1.24 (0.84-1.81)	1.51 (1.00-2.30)[b]

Abbreviations: CI = confidence interval; HbA1c= glycated hemoglobin; IL.
[a] All models are adjusted for age, sex, obesity, nursing home residency, history of chronic obstructive pulmonary disease, atrial fibrillation, cardiovascular diseases, CURB-65 of ≥3, and hypoxemia.
[b] Indicates statistical significance.

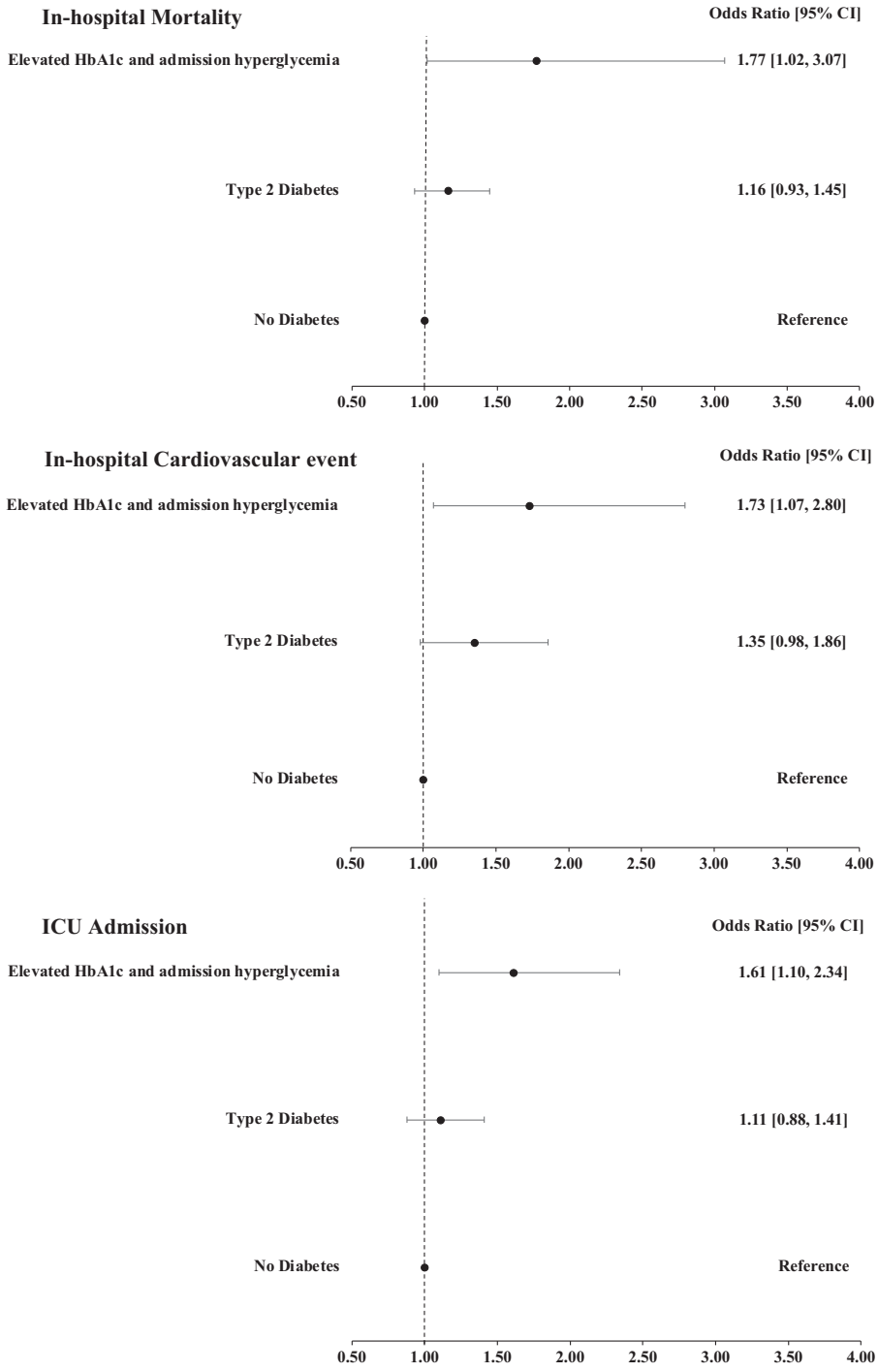

Fig. Forest plots of the association between elevated glycated hemoglobin levels and/or admission hyperglycemia, type 2 diabetes, and no diabetes with SARS-CoV-2 pneumonia outcomes. CI = confidence interval; ICU = intensive care unit; HbA1c = glycated hemoglobin.

those with elevated HbA1c levels and/or admission hyperglycemia. Interestingly in our study, despite the comparable HbA1c levels, the outcomes were much worse in those with elevated HbA1c levels and/or admission hyperglycemia than in those with type 2 diabetes. Given its ability to determine glucose variability during acute illnesses, admission hyperglycemia can have a more predictive value than HbA1c.[11] We speculate that admission hyperglycemia on the background of an acute on chronic inflammatory state can facilitate cytokine storm[18] and precipitate cardiometabolic complications predisposing the patients with elevated HbA1c levels and/or admission hyperglycemia to poor prognosis. As reported by another study,[19] the inflammatory marker levels (Table 2) were homogeneously elevated in patients with hyperglycemia regardless of the diabetes diagnosis. Considering the complex interplay of acute glucose variability and adverse prognosis,[20] further research involving in-hospital continuous glucose monitoring to evaluate glycemic variability is warranted. In addition, delayed diagnosis due to the lack of access to health care amid the pandemic may contribute to poor prognosis in patients with elevated HbA1c levels and/or admission hyperglycemia or prediabetes.

Our study has several strengths. To the best of our knowledge, this is the first study to show the association between patients with

elevated HbA1c levels and/or admission hyperglycemia and cardiovascular outcomes in SARS-CoV-2 pneumonia. The data for this study came from a large multicenter retrospective cohort study that collected electronic medical data in the metropolitan area. In addition, the demographic characteristics, socioeconomic trends, and health behaviors of the population of the city of Louisville can be generalized to the United States.[21]

There are also a few limitations to acknowledge. The results of this retrospective study may not be generalizable to nonhospitalized patients because their characteristics may be significantly different from patients with SARS-CoV-2 pneumonia requiring hospitalization. The findings of this study may also not be applicable to patients with type 1 diabetes because they were excluded from the analysis. The small sample sizes within subgroups affected the precision of the estimates, resulting in wide CIs. Because of the timeline of the present cohort, our study did not capture the streamlined changes in the standard of care, including availability of monoclonal antibodies and vaccines, as the pandemic evolved. We did not assess the markers of cardiac injury and electrocardiogram and echocardiogram findings. Furthermore, heart failure reported under the cardiovascular events was not classified as heart failure with reduced ejection fraction or heart failure with preserved ejection fraction.

Conclusion

Patients with elevated HbA1c levels and/or admission hyperglycemia hospitalized with SARS-CoV-2 pneumonia are at higher risk of developing acute in-hospital cardiovascular complications and death than those with type 2 diabetes and no diabetes. Implementing health care-wide strategies for aggressive screening and early intervention of prediabetes and diabetes can improve outcomes in the current and future pandemics.

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Author Contributions

J.R. and F.A. designed the study; S.K., D.S., T.A., S.F., J.R., and F.A. interpreted the data; S.K., T.A., and V.C. performed the statistical analysis; J.R. and F.A. supervised the study; D.S. and T.A. drafted the manuscript; A.A., V.S., U.A., and D.C. wrote the sections of the manuscript; and S.K. and D.S. edited the manuscript. All authors critically reviewed the manuscript before approving the final draft. S.K. takes responsibility for the content of the manuscript, including the data and analysis.

Disclosure

The authors have no multiplicity of interest to disclose.

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